

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

STATUS OF CLAIMS

Claim 90-111 are pending. Claims 90 and 99 have been amended.

A detailed listing of all claims that were in the application is presented with an appropriate defined status identifier, regardless of whether the claims remain under examination in the application. Upon entry of this amendment, claims 90-111 will remain pending. No new matter has been added.

1. Suspension of Prosecution

The PAIR report for the present application contains two entries erroneously attributing suspension of prosecution to the applicants. PAIR contains an entry dated 07-06-2005 titled: "Mail Letter Suspending Prosecution at Applicant's Request" and entry dated 07-02-2005 titled: "Letter of Suspension – Applicant Initiated."

Applicants did not request a suspension of prosecution at any time and any activities that resulted in suspension was solely due to the Office's delays. Accordingly, the entries of 07-06-2005 and 07-02-2005 should be corrected to state that suspension was initiated by the Office, not Applicants.

2. Provisional obviousness-type double patenting rejection over Application No. 09/159,105

The Office provisionally rejected claims 90-111 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-177 of Application No. 09/159,105.

The '105 application is abandoned. Applicants submit that the rejection is moot and respectively request reconsideration and withdrawal of this rejection.

3. **Provisional rejection over U.S. 5,721,256 or 5,874,449 or 5,968,957 in view of Application No. 09/159,105 and Feghali et al.**

The Office stated “Claims 90-111 are provisionally rejected under 35 U.S.C. § 103(a) or under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the reference of the claims of Hamilton et al U.S. 5,721,256 or 5,874,449 or 5,968,957 in view of Application No. 09/159,105 and Feghali et al. [MEDLINE 98242495]” because the patents allegedly “disclosed all the elements of the claims except the neurotrophic agent.” Office Action, p. 2, para. #3.

Applicants submit that the compounds claimed in the cited patents are structurally distinct from those presently claimed and Application No. 09/159,105 is abandoned and therefore not available as prior art. The Office applied Feghali solely for its disclosure “that sensorineural hearing loss is a neurological disorder treatable by neurotrophic factors” (Office Action, p. 2, para. 2) and consequently fails to cure the deficiencies of the primary references.

U.S. 5,721,256 and U.S. 5,968,957 require a keto, carboxylic ester, or carboxamide moiety adjacent to the ring nitrogen. The compounds of the present claims do not require such a moieties.

U.S. 5,874,449 requires a $-(C=O)-S-$ moiety or a $-(C=S)-S-$ moiety (i.e., a thioester moiety) adjacent to the ring nitrogen. The compounds of the present claims do not require such moieties.

Accordingly, there is no overlap between the present claims and the claims of U.S. 5,721,256 or U.S. 5,968,957 or U.S. 5,874,449.

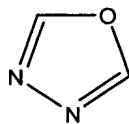
The Office cites Application No. 09/159,105 for its disclosure of neurotrophic factors and states that it “would constitute a 102(e) reference when the claims become allowable” (Office Action, p. 2, para. 2, and p. 3, ll. 10-11). As noted above, Application No. 09/159,105 is abandoned. Application No. 09/159,105 never published. Accordingly, Application No. 09/159,105 is not available as prior art under § 102(e) against the present claims.

Applicants request that the Office withdraw this ground of rejection.

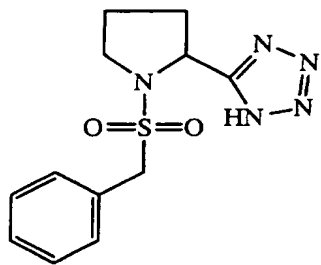
4. **Rejection over U.S. 5,721,256 in view of King or Patani**

Claims 90-111 are rejected under the judicially created doctrine of obviousness-type double patenting over claim 13 of U.S. 5,721,256 in view of King or Patani. Applicants respectfully traverse.

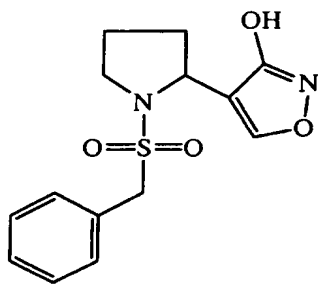
The Office referred to “the species of claim 96, p.6, the 2-ethyl-1,3,4 oxadiazol-5-yl compound.” Office Action, sentence bridging pp 3-4. The Office apparently asserted thereby that claim 96 recites such a compound. However, claim 96 recites 3 compounds, none of which bears a 2-ethyl-1,3,4 oxadiazol-5-yl moiety, i.e., none contains an 1,3,4-oxadiazolyl moiety. For the examiner’s convenience, Applicants reproduce below the structures of oxadiazole and the 3 compounds of claim 96:



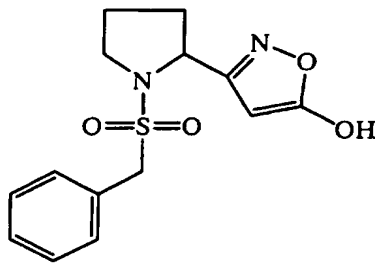
1,3,4-Oxadiazole



;



; and



Compounds of claim 96

As to the relevance of the King and Patani references, the Office apparently relies on these references to support the premise that “modified compounds under the bioisosterism

principle is well recognized to have the same utility as the lead compound” (Office Action, p. 4, ll. 8-10).

Applicants respectfully submit that the King and Patani references themselves contradict the Office’s assertion by casting doubt on the predictability of success in bioisosteric replacement. Far from disclosing the bioisosteric groups are interchangeable in drugs to retain identical pharmaceutical activity, these references present the biosisosterism principle as an alternative “rational” drug discovery strategy. Specifically, these references state:

Three of the standard methodologies that the medicinal chemist can use as “rational” approaches to lead optimization form the basis of this chapter. These are bioisosteric replacement, conformational restriction, and pro-drug formation.

...

Bioisosteres, however, are substituents or groups that do not necessarily have the same size or volume, but have a similarity in chemical or physical properties which produce broadly similar biological properties. It is therefore unlikely that bioisosterism will produce marked increases in potency; however **significant changes in selectivity, toxicity, and metabolic stability could be expected.**

...

When considering any approach to lead optimization, alteration of one part of the molecule almost always affects more than just one property. Isosteric and bioisosteric replacements are no exception and this should always be considered when analyzing the result of such replacements. For example a simple CH₂ to O to S series of replacements can alter size, shape, electronic distribution, water or lipid solubility, pK_a, metabolism, or hydrogen bonding capacity, all with **unpredictable effects upon biological activity.**

King, p. 207, ll. 12-15 and 28-32, and p. 209, ll. 1-7.

Bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents. **The concept of bioisosterism is often considered to be qualitative and intuitive.**

...

As can be the case for any bioisostere, not all of these replacements will necessarily result in a compound with comparable biological activity to the template drug.

Patani, p. 3147, left col. l. 2 from bottom, to right col., l. 4, and p. 3165, left col. ll. 21-24.

Asserting obviousness based on speculative bioisosterism alone is a classic example of applying the impermissible “obvious to try” standard of obviousness. *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (what would have been “obvious to try” would have been . . . to vary all parameters or try each of numerous possible choices . . . where the prior art gave . . . no direction as to which of many possible choices is likely to be successful [or] . . . to explore . . . a promising field of experimentation, where the prior art gave only general guidance). See *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986) (structural similarity, prior art suggestion of claimed anti-depressant activity of claimed compounds, and a suggested bioisosteric relationship together yield a *prima facie* case of obviousness).

Here, the compounds are not structural similar, there is no prior art suggestion of activity of the claimed compounds, and there is a tenuous “non-classical” bioisosteric relationship in the relevant moieties.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection under § 103 (a).

5. Rejection under 35 U.S.C. § 112, second paragraph

The Office rejected claims 90-107 for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Independent claims 90 and 99 have been amended to delete the term “carboxylic acid isostere”. Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejection under § 112, second paragraph.

6. Ownership of applications

The Examiner requested clarification of the ownership of the present application and Application No. 09/159,105 (national phase of PCT application WO 99/14998). This issue is now moot because, as noted above, Application No. 09/159,105 is abandoned.

CONCLUSION

Applicants believe that entry of this amendment would place the present application in condition for allowance entry. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the application to allowance.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By 

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